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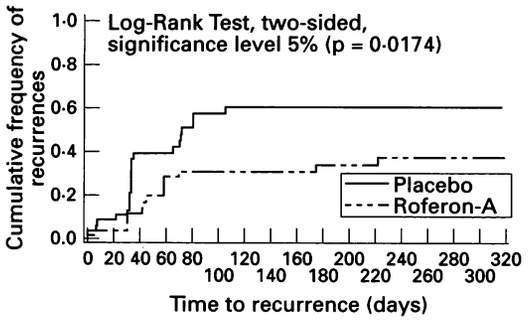
Systemically administered interferon alfa-2a prevents recurrence of condylomata acuminata following CO_2-laser ablation. The influence of the cyclic low-dose therapy regimen. Results of a multicentre double-blind placebo-controlled clinical trial

From placebo-controlled clinical trials it has been concluded that subcutaneous interferon (IFN) alfa-2a is not effective as a monotherapy in the treatment of refractory condylomata acuminata at a dose of 1·5 megaunits if given continuously three times a week for four weeks.[1] Contrasting results, however, have been obtained with IFN gamma given as a monotherapy "cyclically" up to 2 megaunits daily for 7 days, followed by a 4 week pause (1 cycle) for up to 4 cycles.[2] This has led to the hypothesis that either the type of IFN or the treatment regimen were responsible for the differences. In addition, another controlled study administering IFN alfa-2a (3 megaunits/tiw, s.c.) given continuously adjuvantly to CO_2-laser did not show any superiority to placebo,[3] whereas a cyclic application of IFN alpha in an open study showed lower recurrence rates in the IFN group.[4] Therefore, we argued that the therapy regimen used could be the main reason for the observed treatment failure.

In contrast, in our study IFN alfa-2a was given cyclically adjuvent to CO_2-laser, comprising 5 days treatment with 1 megaunit/day and a 4 week treatment-free interval (1 cycle) up to a maximum of 3 cycles, leading to a total of 15 megaunits of IFN alfa-2a. The follow-up lasted 18 weeks. The evaluation of efficacy was done by the comparison of recurrence rates at week 33. A total of 84 patients (equally distributed to the therapeutic arms) were included in the study, out of which 32 (IFN alfa-2a) and 35 (placebo) respectively were evaluated at week 33. At the endpoint of the study 13 out of 32 (41%, 95% confidence interval, 24–59%) of the IFN group and 22 out of 35 patients (63%, 95% confidence interval 45–79%) of the placebo group showed a recurrence of the condylomata. This difference is significant at a level of significance of 5% (χ^2 = 3,312, critical value for one-sided testing at 5% level: 2,076). Figure 1 shows the cumulative frequency of recurrence of the condylomata in relation to time after surgery. The log rank two-sided test revealed statistically significant differences at a 5% level (p = 0·0174). The treatment was generally well tolerated. Eight patients from each group (19%) complained of side effects, usually mild to moderate. No drop outs due to side effects were observed.

Summarising our data, it seems that cyclic application of low dose IFN alfa-2a adjuvant to CO_2-laser ablation is superior in the treatment of condylomata acuminata compared to adjuvant continuous application of interferon or placebo, both in terms of recurrence rate and time to recurrence.



Cumulative frequency of recurrences of condylomata acuminata after treatment with interferon alfa-2a (Roferon®-A) and CO_2-laser in relation to time to recurrence.

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Herpes simplex virus infection in women: viral subtypes and epidemiological features in a district hospital

The incidence of genital herpes is reportedly on the increase in many parts of the UK,[1-4] and herpes simplex virus type 1 (HSV 1) has become the predominant subtype in genital infections in women.[2-5] Reasons for the apparent increase in genital herpes in general, and HSV 1 in particular, are as yet unclear.

The aim of this study was to describe the proportions of HSV types 1 and 2 in women presenting with a first symptomatic episode of genital herpes at our genitourinary medicine (GUM) clinic; and compare clinico-epidemiological features of the two subtypes of HSV.

All women (n = 121) with a first sympto-

matic episode of genital herpes infection presenting to the GUM clinic at North Staffordshire hospital between January 1994 and May 1995 were included in the study. HSV was isolated on either MRC-5 or Vero cell monolayers (BioWhittaker, UK); and typed by Direct Immunofluorescence assay, using FITC conjugated monoclonal antibody against HSV 1 and 2 (PHLS, London). Demographic, microbiological and clinical information obtained from patients' clinical notes was analysed using Epiinfo statistical software. The chi square test was used to determine statistical significance.

The table summarises the main clinical and epidemiological findings. Women with HSV types 1 and 2 were comparable in all other features except mean age and mode of referral (table). Patients with either type of HSV had a low prevalence (4%) of concurrent STD (compared with other STD patients in our clinic[6 7]): Chlamydia-1, Trichomoniasis-1, genital warts-3. Sixteen patients (14%) had a past history of STD, 7 and 9 of them had HSV 1 and 2, respectively. Of 118 women for whom information was available, 17 (8 with HSV 1 and 9 with HSV 2) gave a personal history of labial herpes. Similarly, only 27 out of 101 respondents had partners who suffered from "cold sores". There was no association between reported history of herpes labialis in sexual partner and HSV type, p = 0·06.

The proportion of HSV types 1 and 2 has remained relatively stable in our catchment population over the last 10 years. In 1985/86, HSV 1 and 2 each accounted for 50% of genital herpes infections in women in our clinic (Stocker DI, unpublished data). Thus the proportion of HSV 1 in women in our clinic was initially higher than some other clinics in the UK,[1 5] but has apparently remained stable and has since been overtaken by other clinics.[2-4]

HSV 1 and 2 seem to have similar clinical and epidemiological features, at least in women. For both viral subtypes most patients were in stable sexual relationships (table) and the prevalence of concomitant STD was very low (4%). However, women with HSV 1 were younger (p < 0·002); and more likely to be referred by their general practitioner (p < 0·02) than women with HSV 2. Scoular *et al*[5] also found a high proportion of women aged 25 years or under among women with HSV 1 infection. Possible explanations for younger patients with HSV 1 include: low herd immunity in socially privileged societies, changes in sexual practices which favour oral-genital transmission and autoinfection. Nageswaran *et al*[8] noted that women with HSV 1 were more likely to consult their general practitioner prior to GUM clinic attendance. In that study, self-referred patients (mostly with HSV 2) were more likely to have had an STD before. Past history of STD was comparable in our patients with HSV 1 (12%) or HSV 2 (15%). However, women aged 25 years or under were more likely to consult their general practitioner first; accounting for 72% of 67 general practitioner referrals compared with 49% of 39 self-referrals, p < 0·01. Hence younger age could explain the larger proportion of general practitioner referrals among women with HSV 1 than HSV 2 infection in our study.

That 57% of our patients had been referred by their general practitioner suggests that such referral habits may influence GUM clinics' HSV morbidity statistics. For example over 20% of patients with first-episode genital herpes may be treated in the community by their general practitioner and some of those referred to GUM clinics, may be started on treatment.[9] Do women who consult their general practitioner first with genitourinary symptoms do so because they prefer to be treated in the community or because they are unaware of GUM clinics? As most of our patients referred by general practitioners were young, it is possible that, owing to greater awareness of teenage sexual health generated by "The Health of the Nation" document, general practitioners are more likely to refer younger patients with genitourinary symptoms to the GUM clinic. Also, younger women in stable sexual relationships, without a history of STD, might not attribute genitourinary symptoms to STD and present to their general practitioner instead of GUM clinics.

In our clinic, HSV infection in women seems to be different from other STDs in that most patients are in stable sexual relationships and the prevalence of other concurrent STDs is very low. Unlike Ross *et al*[1] who reported concomitant gonorrhoea in patients with HSV 2 but not HSV 1, none of the HSV infected women in our study harboured *N gonorrhoeae*. Although a recent serological survey found a higher prevalence of HSV 2 among GUM clinic attenders than blood donors,[10] and others have noted differences in prevalence of other concurrent STD[1] or past history of STD[8] between patients with HSV 1 and 2; in our study concurrent or past STD was comparable and very uncommon in women with either HSV 1 or 2. Is symptomatic HSV infection then a disease for those with low risk of other STD in our catchment population?

Epidemiological and clinical features

Feature	*HSV 1*	*HSV 2*	*p value*	*Total*
Number (%)*	62 (51)	59 (40)		121
Age distribution mean (years (SD))	24 (6·5)	28·7 (9·8)	0·002	26·3 (8)
16–19	14 (22·6)	7 (12·3)	NS	21 (18)
20–25	28 (45·2)	23 (40·4)	NS	51 (42)
26–40	17 (27·4)	19 (33·3)	NS	36 (30)
> 40	3 (4·8)	8 (14·0)	NS	11 (9)
Last coitus (days)				
1–7	42 (70)	29 (54)	NS	71 (62)
8–14	16 (27)	15 (28)	NS	31 (27)
> 14	2 (3)	10 (18)	NS	12 (11)
Onset of symptoms (days)				
1–3	17 (35)	9 (21)	NS	26 (26)
4–7	26 (54)	26 (62)	NS	52 (52)
> 7	5 (11)	7 (17)	NS	12 (12)
Sexual partners past 3 months mean (SD)	1·1 (0·3)	1·3 (0·9)	NS	1·2 (0·7)
Regular only	58 (95)	46 (81)	NS	104 (88)
Casual only	1 (2)	1 (2)	NS	2 (2)
Regular & casual	2 (3)	10 (17)	NS	12 (10)
Mode of attendance				
Self-referral	17 (28)	24 (41)	NS	41 (34)
GP referral	41 (67)	27 (47)	0·02	68 (57)
Other	3 (5)	7 (12)	NS	10 (9)
Occupation				
Employed	33 (55)	44 (76)	NS	77 (65)
Student	13 (22)	5 (9)	NS	18 (15)
Unemployed	14 (23)	9 (15)	NS	23 (20)

SD = Standard deviation; NS = statistically significant.
*Unless specified otherwise, figures in parentheses denote percentages.

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Successful treatment of donovanosis with ciprofloxacin

Antibiotic treatment of donovanosis has been empirical, and includes tetracycline,[1] chloramphenicol[2] and cotrimoxazole.[3] More recently, workers in Australia have described successful use of daily injections of cefriazone.[4] Treatment has sometimes depended on the responsiveness of the organism to the antibiotic available in the geographical area concerned.[5] The causative organism, *Calymmatobacterium granulomatis*, a gram negative encapsulated bacterium is difficult to grow on artifical media thus limiting in vitro antibiotic sensitivity studies.

We have succesfully treated donovanosis with ciprofloxacin and report our first case. A 38 year old male from Zambia presented with a ten day history of two painless ulcers on the penis, and no other complaints. He had been in a relationship for one year with his girlfriend, who was in Zambia. Their last sexual intercourse was three weeks prior to presentation. He denied having any other sexual partner during this year.

General examination was unremarkable. His skin and oral mucosa showed no abnormality. He had swollen non tender right inguinal lymph nodes and two ulcers on the prepuce, each about a centimeter in diameter which were clearly demarcated, had thickened edges and minimal granulation tissue. Dark ground microscopy, serological tests for *Treponema pallidum*, culture for *Haemophilus ducreyi*, and herpes simplex virus cell cultures were performed. Five days later, the penile ulcers had increased in size, still with well defined edges (fig 1). Dark ground microscopy for *T pallidum* was again negative. We suspected donovanosis and a biopsy of the edge of one of the ulcers was performed. The patient was started on a two week course of oxytetracycline 500 mg qds orally, but on its completion there was no notable change in the size or appearance of the ulcers. The result of the initial investigations were all negative, but donovanosis was identified on a Giemsa stained specimen (fig 2) and confirmed on histology. In view of this failure to respond to oxytetracycline, we decided to try him on ciprofloxacin, since this has a wide spectrum of activity and is particularly active against gram negative organisms. Commencement on ciprofloxacin 500 mg bd orally was followed by a marked response in the first 7 days, and complete re-epithelisation of the penile ulcers within 2 weeks.

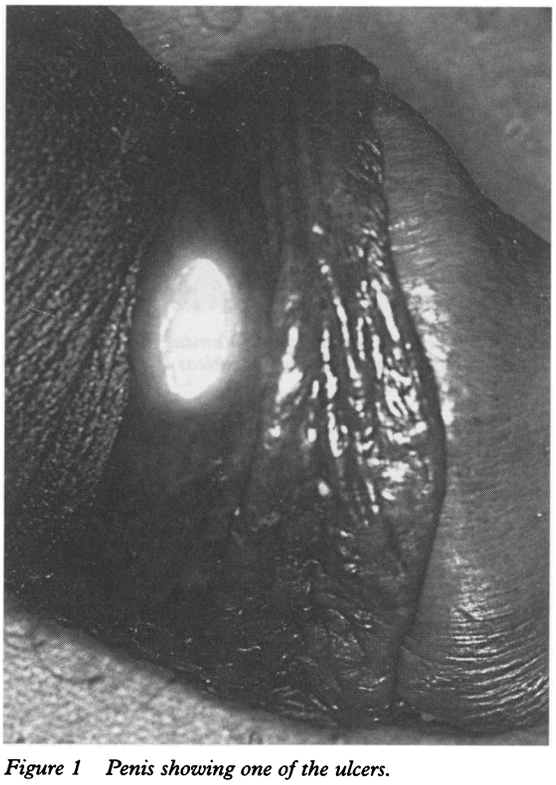

Figure 1 Penis showing one of the ulcers.

Following this experience, we have successfully used ciprofloxacin as first line treatment in two other patients with genital ulcers cytologically and histologically confirmed as donovanosis. These patients also experienced complete re-epithelisation of their genital ulcers within 2 weeks of starting ciprofloxacin. None of the patients reported any adverse effect from the drug. We would recommend ciprofloxacin as drug of first choice in the treatment of early donovanosis, since it it very effective, inexpensive, and relatively free from adverse effects.

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